Georgia Tech Sponsored Research

Project	B-13-634
Project director	Guldberg Robert
Research unit	GRA
Title	Mechanical Properties of a New Biomaterial
Project date	6/30/1999

GEORGIA RESEARCH ALLIANCE

Technology Development Partnership

FY99 Final Project Report

Due Friday, August 27, 1999

B-13-634

B-13-634
#2

Project Number: TDP99.013

Project Title: Mechanical Properties of a New Biomaterial

Project Director: Dr. Robert Guldberg Institution: Georgia Tech

Phone: 404 894-6589 FY99 TDP Funds Received: $40,000

E-Mail: robert.guldberg@me.gatech.edu

Other Project Team Members:

Name	Institution	Phone

Industry Co-sponsor(s):

Name	Company	Phone
David Ku	Restore Therapeutics	404/892-0888

Industry Co-sponsor(s) Approval (to be signed by authorized representative of co-sponsor):

I have read this report and agree with its contents.

Signature: David M. Ku Date: 8/24/99

Signature: _____ Date: _____

Signature: _____ Date: _____

Georgia Research Alliance Technology Development Partnership: Annual Report
FY99 Final Project Report
8/27/99

1. The purpose of our project was to characterize the material properties of a new hydrogel biomaterial developed at Georgia Institute of Technology and commercialized by Restore Therapeutics, Inc. The biomaterial is mechanically similar to the body's soft tissues and may distribute the forces at a joint in a manner very similar to native cartilage. The technology therefore has promise as a cartilage implant for use in millions of patients with degenerative joint diseases and arthritis who are disabled and live in pain. The projected market for a biocompatible, mechanically strong cartilage prosthesis is over $2 billion. The testing we have performed is necessary for Restore Therapeutics to assess the ability of this material to replace the function of cartilage under in vivo loading conditions and our results will be used to significantly improve the long term performance of the biomaterial.

2. The start date of this project was delayed until January 1, 1999 due to negotiations between Georgia Institute of Technology and Restore Therapeutics regarding potential intellectual property resulting from this work. However, most of our original objectives have been met and the remaining objectives will be met by the end of the year. We had three primary objectives: to determine material and failure properties under compression loading, to determine material and failure properties under shear loading, and to develop an image-based rapid prototyping approach to create patient specific bone molds for the material.

   The questions to be addressed by the first objective were:

   A. What is the tangent modulus of the PVA biomaterial at physiologic strains and how does it compare with native cartilage?
   B. Is the tangent modulus strain rate dependent?
   C. What is the strain level of non-recoverable plastic deformation?
   D. What are the recovery and stress relaxation time constants?

   Each of these questions has been addressed. We found that the tangent modulus was very dependent on strain and strain rate and ranged from 1-18 MPa. We have spent considerable time defining the failure properties of the material and have determined that the strain level of non-recoverable plastic deformation is approximately 60-65%. The material displays nonlinear, viscoelastic (i.e. time-dependent) properties very similar to those of native cartilage. As such, we observed significant stress relaxation following application of a constant deformation and determined that recovery occurred over a period of approximately 20 hours. This work has led to the submission of abstracts to the Biomedical Engineering Society (BMES) Meeting in October, 1999 and the Orthopaedic Research Society (ORS) Meeting in March, 2000. The BMES abstract was accepted for a podium presentation. Copies of both abstracts are appended to this report.

The questions to be addressed by the second objective were:

A. What is the shear tangent modulus of the PVA biomaterial?
B. Is the shear tangent modulus strain rate dependent?
C. What are the yield and ultimate failure stress levels in shear?
D. Does failure occur at the interface or within the PVA biomaterial?

A testing fixture has been designed and built to conduct the shear testing of the hydrogel and these tests are currently being performed. We expect the shear testing to be complete by the end of 1999.

The questions to be addressed by the third objective were:

A. Can a 3D mold of a bone metaphysis be created using patient image data and rapid prototyping techniques?

We have met this objective. We developed a protocol to transform 3D image data of a patient's joint into a surface model of the bone. The surface model was written in a format that is compatible with rapid prototyping systems that build 3D complex structures layer by layer out of epoxy resin. Working with the Rapid Prototyping Manufacturing Institute (RPMI) at Georgia Institute of Technology, we then built a mold of a distal femoral condyle that could be used to create a patient-specific layer of hydrogel for cartilage replacement.

3. The technical methods utilized in this study and resulting data are documented in the two attached research abstracts.

4. The results of this study will be used by the company to develop improved formulations of their biomaterial for specific use as a cartilage replacement. Our intent has been to develop a series of well-defined tests that will be used to assess each new formulation. Multiple tests are required since a formulation that is stiffer in compression may for example possess decreased failure properties. Thus, the developed methods will be used to optimize the biomaterial for use as a cartilage replacement.

5. This collaborative project has helped to support the development of a product for a start-up biotechnology company in Georgia. Given the strengths of Emory and Georgia Tech in biotechnology, the Atlanta area is a natural location for the start-up of such companies. A nucleus of successful biotechnology companies will attract others to the Atlanta area.

6. The next step is to complete our evaluation of the material in shear and then begin testing the compressive, failure, and time-dependent properties of different formulations. Additional future work will require developing methods to adhere the material to bone and finally testing of the material in an in vivo model prior to human clinical testing.

7. This work was supported equally by the Georgia Research Alliance and Restore Therapeutics. The materials testing system utilized to complete the work was funded by the School of Mechanical Engineering, the Whitaker Foundation,

Restore Therapeutics, and the Institute for Bioengineering and Bioscience.

8. The funding provided by the Georgia Research Alliance was utilized to support the efforts of a graduate student and three undergraduate students working on the project ($13,381). The remainder of the funding was used to purchase materials and supplies as well as equipment needed to conduct the study. A detailed financial spreadsheet is appended to this report

9. For this project, the Technology Development Partnership program effectively fostered an academic-industry interaction that has benefited both parties. Restore Therapeutics has received information that will improve the performance of their biomaterial product. The funding for this project also helped train a graduate student in my laboratory and provided a laboratory research experience for three undergraduate students, one of whom has subsequently decided to pursue a Ph.D. in Biomedical Engineering at Georgia Institute of Technology.

MECHANICAL PROPERTIES OF A NOVEL HYDROGEL FOR THE REPLACEMENT OF DAMAGED ARTICULAR CARTILAGE

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ABSTRACT: A novel hydrogel has been developed to potentially replace damaged articular cartilage. The purpose of this study was to quantify mechanical properties of the hydrogel relative to those of native articular cartilage. Preliminary tests have shown that the material possesses similar viscoelastic properties to that of natural cartilage.

INTRODUCTION: Osteoarthritis can cause severe knee and joint pain that can lead to life-long disabilities. Among the over 100 different types of arthritis conditions, osteoarthritis is the most common, affecting over 15 million people in the United States alone. Presently, the only proven surgical therapy for patients with debilitating osteoarthritis or trauma is total knee replacement. Risks of total knee replacement include blood clots in the legs that can travel to the lungs (pulmonary embolism), chronic knee pain and stiffness, and infection of the knee.

An alternative to total knee replacement might be to replace the damaged cartilage with a strong biomaterial that possesses biocompatible properties. If this could be implanted arthroscopically, patient morbidity, cost, and recovery time would be decreased significantly.

A novel and versatile hydrogel has been developed. The hydrogel has many potential applications, one of which is the replacement of damaged articular cartilage. The purpose of this study was to quantify mechanical properties of the hydrogel relative to those of native articular cartilage.

METHODS: Hydrogel sheets were subjected to a compressive load applied by a plane-ended, smooth, non-porous, cylindrical indentor. The sheets had an average thickness of 3.08 mm and were cut into circular testing coupons 20 mm in diameter. The indentor had a diameter of 3.0 mm and traveled at a speed of 10 mm/min. Force (N) and indentation depth (mm) were recorded (n=3).

An unconfined compression test was repeated at four strain rates: 0.2, 0.4, 0.6, and 1.2 mm/s. The diameter and height of the specimens were measured with a standard calipers to be 6.35 mm (1/4"). The specimens were preconditioned at a 0.4 mm amplitude over 10 cycles at 1 Hz. The samples were then loaded in compression to a maximum displacement of 1.2 mm (20% strain), a range over which load-displacement data was acquired.

RESULTS: The compression modulus using indentation testing at 10 mm/min was found to be 2.06±0.07 MPa @ 20% strain, 3.43±0.09 MPa @ 40% strain, and 7.34±0.24 MPa @ 60% strain (Figure 1). Figure 2 shows an increase in modulus from 1.13 MPa (0.2 mm/s) to 1.34 MPa (1.2 mm/s), which indicates strain rate dependency (r^2=0.97). The stress-strain curve in Figure 1 shows an increasing stiffness at higher strain levels. Both Figure 1 and 2 show that the material is linearly elastic below 20% strain.

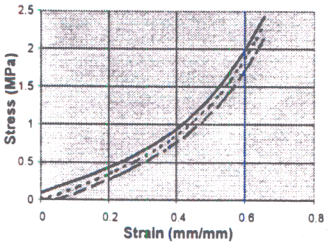

Figure 1: Indentation

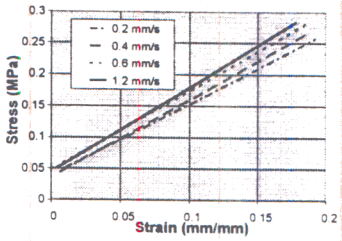

Figure 2: Unconfined Compression

DISCUSSION: A primary motivation for this study was to quantify the hydrogel mechanical properties relative to those of natural articular cartilage, thereby optimizing its potential function as a cartilage replacement biomaterial. The water content of this hydrogel and natural cartilage are similar (75%), and the compressive modulus of the hydrogel is comparable to that of natural articular cartilage (0.5-1.4 MPa) at low strain rates, demonstrating its viscoelasticity [1].

The results shown are preliminary, with tests being done before any optimization of the hydrogel formulation. Even so, it is observed that the biomaterial shows a strain hardening response typical of cartilage and other biological tissues.

In addition to optimization of properties such as elastic modulus, ultimate strength, hydraulic permeability, and fatigue strength, current and future research will include optimizing adherence of the biomaterial to bone surfaces and designing anatomic molds to provide off-the-shelf availability for patients.

ACKNOWLEDGEMENTS: This work is co-sponsored by Restore Therapeutics and the Georgia Research Alliance.

REFERENCE:

1) JA Buckwalter and VC Mow. Cartilage Repair in Osteoarthritis. In *Osteoarthritis: Diagnosis Medical/Surgical Management*, 2nd Ed. W.B. Saunders Co. (1992): pp. 71-107.

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Preferences and Keywords

Biomaterials;mechanical properties;cartilage graft;failure;articular cartilage

Disclosure

ABSTRACT NO. _____
PAPER NO. _____

TIME-DEPENDENT AND FAILURE PROPERTIES OF A PVA HYDROGEL IN UNCONFINED COMPRESSION

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INTRODUCTION

Polyvinyl alcohol (PVA) hydrogels have been investigated as a potential biomaterial replacement for damaged articular cartilage [1]. PVA hydrogels possess a high water content similar to cartilage tissue and have been shown to be highly biocompatible. However, a biomaterial substitute for articular cartilage must also exhibit sufficient mechanical properties to restore normal function to damaged joint surfaces. While the biocompatibility attributes of PVA hydrogels have been well documented, the mechanical behavior of these materials relative to cartilage tissue is not well understood.

Articular cartilage displays viscoelastic material behavior, including time, rate, and history dependence, hysteresis, stress relaxation, and creep. The major physical mechanism producing this behavior is the frictional drag caused by interstitial fluid flow through the porous permeable solid matrix. Although hydrogels can be made to approximately mimic the porosity and water content of cartilaginous tissue, the interaction between the two phases is likely to be quite different. To assess the potential for a biomaterial to replicate cartilage function, it is necessary to determine time dependent and failure properties in addition to compressive modulus.

A recently developed PVA hydrogel (Restore Therapeutics, Atlanta, GA) possesses nonlinear stress-strain behavior and a compressive tangent modulus of 1-20 MPa in the elastic regime (Fig. 1). The purpose of the current study was to extend the evaluation of this biomaterial by quantifying time-dependent and failure properties in unconfined compression.

METHODS

All tests were performed in unconfined compression on cylindrical samples of PVA hydrogel measuring 6 mm in diameter and length. The dimensions of each sample were measured optically before and 24 hours after testing using a 2X microscope objective and image analysis software. Samples were submerged in deionized water and maintained at 37° C during testing. Preconditioning cycles were applied from 1 to 10 N prior to all tests.

The compressive tangent modulus of the hydrogel was found by applying compression ramps via a flat platen at rates of 6, 60, and 600 mm/min (n=12 for each) up to 65% strain. The tangent modulus was calculated by using a linear fit of localized stress-strain data at six normalized strain levels (10 - 60%).

Plastic failure of the material was determined by applying two consecutive compressive ramps to samples in 5% increments from 25% to 80% strain at a rate of 6 mm/min (n=12). Energy dissipation was determined by calculation of the area between the load and unload curves. The three failure criteria used were: 1) a dramatic increase in hysteresis from previous strain levels, 2) a residual displacement in the loading part of the second cycle, and 3) visual observation twenty-four hours after testing [2]. Hysteresis was calculated as energy loss per unit volume, and the residual displacement was determined through comparison of the peak stress of the two cycles at the same strain.

Stress relaxation was done by applying an initial deformation of 20% strain to the specimen, and then holding for 1200 minutes (20 hrs) (n=4).

RESULTS

The nonlinearity of the PVA hydrogel led to an increase in the average tangent modulus from 1.1 ± 0.2 MPa at 10% strain to 18.3 ± 2.0 MPa at 60% strain. As expected, the modulus was also found to be strain rate dependent. Figure 2 shows the tangent modulus at 30% strain significantly increased from 2.6 MPa at 6 mm/min to 3.6 MPa at 600 mm/min ($P < 0.0001$). Using hysteresis, peak stress reduction between consecutive testing cycles, and visual observation following a 24 hour recovery as failure criteria, it was estimated that the onset of plastic deformation occurred around 60-65% strain (Figure 3). Application of a constant 20% strain resulted in a stress relaxation response from a peak of 0.24 ± 0.01 MPa to an equilibrium level of 0.08 ± 0.004 MPa (Figure 4).

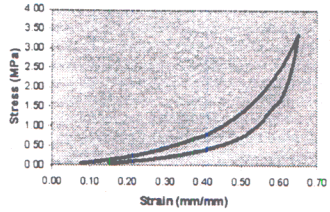

Figure 1: Stress-Strain Behavior

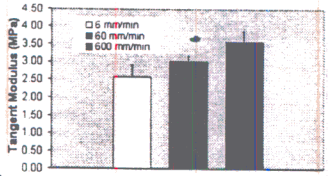

Figure 2: 30% Tangent Modulus

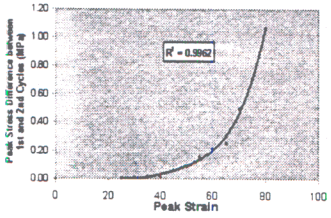

Figure 3: Plastic Deformation

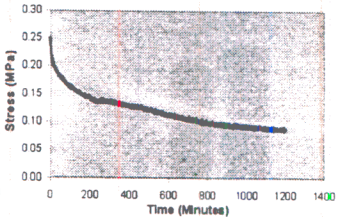

Figure 4: Stress Relaxation

DISCUSSION

The PVA hydrogel exhibited nonlinear, viscoelastic behavior similar to soft biological tissues. The tangent modulus increased exponentially with strain and was comparable to that of articular cartilage under physiological loading conditions [1,3]. Although a consistent hydrogel formulation was used for this study, manufacturing parameters may be altered to modify water content and cross-linking, thereby adjusting material properties.

Strain rate was found to be a significant determinant of tangent compressive modulus. The modulus increased 38.5% over two orders of strain rate magnitude, representing a moderate yet statistically significant increase. Further investigation of the response to impact loading is necessary for a complete evaluation.

The plastic failure strain is an important consideration because it correlates to the maximum stress the material can withstand without losing its ability to recover. The hydrogel failure strain of 60-65% corresponds to 2.4-3.9 MPa, which is above the range of physiological joint stresses occurring at low strain rates [4]. Further testing is required to determine how the failure level changes with both impact loading and cyclic fatigue, thus characterizing the strain rate dependence of the failure range.

Ongoing work includes fitting stress relaxation data to theoretical models, fatigue testing, and investigating shear properties of the hydrogel. Our data suggest the hydrogel exhibits comparable properties to those of articular cartilage in terms of tangent modulus and failure; however, further evaluation is necessary to assess its potential to replace damaged cartilage tissue.

ACKNOWLEDGEMENTS

This work is co-funded by Restore Therapeutics and the Georgia Research Alliance.

REFERENCES

1) Zheng-Qiu G, *et al.* Biomed Mat Eng 8: 75-81; 1998.
2) Kerin AJ, *et al.* Proc Instn Mech Engrs 212 (H): 273-280; 1998.
3) Stammen JA, *et al.* Presented at the 1999 BMES Conference.
4) Barker MK, *et al.* J Biomech 30(4): 377-81; 1997.

B-13-634			R. Guldberg				7/1/98-6/30/99	
TDP:99-013			246R13030A0					
PERSONAL SERVICES								
	BP #	EMPLOYEE Last Name	SALARY Budget	BUD.AMDT	fringe	ENCUMB	EXPEND	BALANCE
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		GRA			0.00			0.00
	2	Stammen, Jason	$10,500.00		0.00		10,499.99	0.01
	3	Student Assistant			0.00	0.00	0.00	0.00
5/19/99		Ok,Seong-Joon					1,200.00	-1,200.00
5/19/99		Thompson,Taryn					1,201.20	-1,201.20
		Lin, Angela					480.00	-480.00
	4		$2,400.00		0.00	0.00	0.00	2,400.00
					0.00	0.00	0.00	0.00
					0.00		0.00	0.00
					0.00		0.00	0.00
		Fringe			$0.00			0.00
		PS Balance	$12,900.00			$0.00	$13,381.19	($481.19)
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		P-Card Totals	$0.00		$0.00	$0.00	$0.00	
								$0.00
M&S			$5,000.00					
Research Notebooks	11/13/98	116963401					72.85	
Cole Parmer		116963402					303.20	
VWR Scientic		116963403					2,382.67	
GT Bookstore		116963407					199.00	
GT Bookstore							29.14	
		M&S Totals	$5,000.00		$0.00	$0.00	$2,986.86	
								$2,013.14
Equipment			$22,100.00					
Shore Western Manf	3/31/99	116963404 void			0.00			
Forma Scientific		116963405					4,327.25	
Savant Instruments		116963406				8,192.80		
System upgrade		116963408				1,000.00		
Ext. Disk subsystem		116963409				1,840.00		
Compaq-configuration		116963410				1,539.00		
Gateway E-4200		116963411				2,669.00		
DDL		116963412				2,400.00		

B-13-634			R. Guldberg					7/1/98-6/30/99	
TDP:99-013			246R13030A0						
PERSONAL SERVICES									
	BP #	EMPLOYEE	SALARY	BUD_AMDT		fringe	ENCUMB	EXPEND	BALANCE
DDL		116963413					1,174.00		
Boston Piazo		116950408					9.90		
GT Bookstore		116935401					460.00		
		Equipment Totals	$22,100.00			$0.00	$19,304.70	$4,327.25	
									($1,531.95)
		Dir BUDGET TOTAL	$40,000.00				TOTAL BALANCE		$0.00
		Indirect	$0.00						$0.00
		Total Budget	$40,000.00						$0.00
			Approp. Ledger Fringe Adjustment						

1. Describe the specific opportunity that your project work addressed. Quantify the problem's impact on your industry co-sponsor. Be specific in describing how and why this project work is important to the co-sponsor.

   Format: one-half page maximum.

2. State your original FY99 project purpose and briefly describe the actual results achieved for each objective/goal during the project. The key is to demonstrate that you set a target at the beginning of the year, and at the end of the year, you know where you stand relative to that target.

   Format: one page maximum.

3. Describe in detail your technical approach and specific project findings and results.

   This portion of your report should document non-confidential technical information, milestone achievements, and implementation steps associated with your project.

   Format: four pages maximum

4. Describe how your results are actually being used by the co-sponsor and what savings or improvements have been realized. What benefits and/or cost savings have they realized? The key here is to demonstrate that the results of this project provide (or will provide in the future) tangible benefits for Georgia companies.

   Format: one page maximum.

5. In three sentences or less, describe what benefit the state of Georgia received from this collaborative project. Be specific and quantitative. [Hint: If you had 15 seconds to explain your work to the Governor, how would you convince him that your work is worthy of funding?]

6. Briefly describe next steps in the development and/or commercialization process. (This applies to completed projects as well as to continuing work funded by this program.

   Format: one-half page maximum.

7. Cost-Share Budget

   Describe in detail how industry or other organizations supported this work.

   Format: one-half page maximum.

8. Financial Accounting

   Provide a full financial accounting of the project including a sources and uses of funds statement.

   Format: one page maximum.

9. What suggestions do you have to improve the effectiveness of the Technology Development Partnership program?

   Format: one-half page maximum.

10. Co-sponsor questionnaire [Pages 4 & 5 are to be completed by the co-sponsor company]

A. Why did your company choose to engage in this program? Select one or more from the following.

- ✓ Access to equipment
- ✓ To establish relationships with the university
- To pursue higher-risk research and development
- Cost-effectiveness
- Access to university ideas
- ✓ Access to university expertise
- Other _____

Comments:

B. What would have happened to this project without the Technology Development Partnership program? Select one or more from the following.

- ✓ Project delay
- ✓ Hire consultant
- Conduct in house
- No project
- Other _____

Comments:

C. What effects did the TDP project have on your company? Select one or more from the following.

- ✓Too soon to tell
- New company formed
- Increased sales
- Solved problem
- Developed new product
- Improved existing product
- ✓Speeded the development process
- Provided cost savings
- Other _____

Comments:

D. What effects did the TDP project have on your company's employment, profits, and competitiveness? Select one or more from the following.

- ✓Too soon to tell
- Increased profits
- New jobs created
- No changes
- ✓Increased competitiveness
- Other _____

Comments: